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(54) Title: HIGH–PRECISION MEASURING METHOD AND APPARATUS PARTICULARLY USEFUL FOR NON–INVASIVELY MONITORING GLUCOSE LEVELS

(57) Abstract: A method and apparatus for monitoring a condition having a known relation to, or influence on, the transit time of a cyclically-repeating energy wave moving through a transmission channel, by: (a) transmitting a cyclically-repeating energy wave through the transmission channel from a transmitter at one end to a receiver at the opposite end; (b) continuously changing the frequency of the transmitter according to changes in the monitored condition while maintaining the number of waves in the transmission channel as a whole integer; and (c) utilizing the changes in frequency of the transmitter to provide a continuous indication of the monitored condition. Operation (b) is preferably performed by detecting a predetermined fiducial point in each cyclically-repeating energy wave received by the receiver, but may also be performed by the use of a phase-locked loop circuit, to maintain the number of energy waves in the loop of the transmission channel as a whole integer.

HIGH–PRECISION MEASURING METHOD AND APPARATUS PARTICULARLY USEFUL FOR NON–INVASIVELY MONITORING GLUCOSE LEVELS

RELATED APPLICATIONS

The present application is related to International Applications PCT/IL00/00241, Publication No. WO 00/67013, and PCT/IL02/00854, Publication No. WO 03/035321, corresponding to US Patents 6,621,278 and 6,856,141; it also includes subject matter of US Patent Application 10/844,398 filed May 13, 2004, and Israel Patent Application 166,760 filed February 8, 2005, the priority dates of which are hereby claimed.

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates broadly to high precision measuring methods and apparatus, and particularly to methods and apparatus for measuring various parameters or conditions having a known relation to, or influence on, the transit time of movement of an energy wave through a medium.

The present invention also relates to a method and apparatus for non–invasively monitoring the concentration of a target substance in a body. This aspect of the invention is particularly useful for measuring the concentration, or changes in the concentration, of glucose within the blood of a person, and is therefore described below with respect to that application, but it will be appreciated that the invention could advantageously be used in many other applications.

As brought out in U.S. Patent 6,621,278, many measuring techniques are known for measuring distance, temperature, and other parameters, but such known techniques generally increase in expense according to the precision desired, and also generally have an upper limit as to the precision practically attainable by the technique. For example, the measurement of distances of meters or kilometers with a precision of microns or fractions of a micron is extremely expensive, if attainable at all. The same limitations apply with respect to measuring temperature, force, and other conditions.

Frequent monitoring of blood glucose level is critical for those suffering from diabetes. Currently, glucose measurements are generally performed by the individual, by pricking a fingertip and applying a drop of blood to a test strip composed of chemicals

sensitive to the glucose in the blood sample. However, this method is very painful and usually inconvenient, particularly when done many times (e.g., 4–7 times) per day as recommended.

It is presently estimated that over 18 million people in the USA suffer from diabetes, and that this number will dramatically increase, to about 24 million in 2010. Considerable research and development has been conducted along many different avenues in an attempt to develop an effective non–invasive glucose monitoring device, as shown by the many technical articles that have been published on this subject and the many patents that have issued. Nevertheless, despite this dramatically increasing need for a method for monitoring blood glucose levels in a non–invasive, painless and convenient manner, and despite the considerable research and development efforts that have been devoted to developing such a device, no such device is yet commercially available, insofar as we are aware, having the accuracy, reliability and repeatability needed for general use.

While this problem is particularly acute with respect to monitoring blood glucose levels, the problem is also present in monitoring the concentration of other constituents of blood, such as cholesterol, or the constituents of urine, or of other biological fluids, industrial fluids, other bodies, etc.

BRIEF SUMMARY OF THE PRESENT INVENTION

The above–cited US Patent 6,621,278 discloses a method of monitoring a condition having a know relation to, or influence on, the transit time of a cyclically–repeating energy wave moving through a transmission channel from a transmitter at one end to a receiver at the opposite end, comprising the following operations:
(a) transmitting a cyclically–repeating energy wave through the transmission channel;
(b) continuously changing the frequency of the transmission according to changes in the monitored condition while maintaining the number of waves in a loop including the transmission channel as a whole integer; and (c) utilizing the changes in frequency of the transmission to provide a continuous indication of the monitored condition.

According to one aspect of the present invention, there is provided a method as set forth above, characterized in that operation (b) is performed by a phase–locked loop circuit having an input from said receiver, and an output controlling said transmitter.

According to another aspect of the invention, there is provided a method as set forth above, characterized in that the frequency of the transmitter is continuously controlled by: connecting a voltage–controlled oscillator to drive said transmitter and also to provide a first input to a phase detector; utilizing the output of said receiver to provide a second input to said phase detector and to produce an output from said phase detector corresponding to the difference in phase between the first and second inputs; and utilizing said output of the phase detector to control the voltage–controlled oscillator to drive said transmitter such that the number of waves in the loop including said transmission channel is a whole integer.

The cyclically–repeating energy wave may be an electromagnetic wave, an acoustic wave, or an acoustic wave generated according to the "photoacoustic effect", i.e., by the impingement of an electromagnetic beam against a target. In a preferred embodiment of the invention described below, the electromagnetic beam is a laser beam which generates a photoacoustic wave for non–invasively monitoring the level of glucose in blood.

According to a further aspect of the present invention, there is provided a method of non–invasively measuring the concentration, or change in concentration, of a target substance within a body, comprising the operations: activating a pulse source to apply to the body a series of pulses of energy highly absorbable by the target substance, as compared to other substances, to heat the body and to generate therein, by the photoacoustic effect, a series of acoustic waves propagated through an acoustic channel in the body at a frequency corresponding to that at which the energy pulses are applied to the body; detecting the acoustic waves to produce an electrical signal having a frequency corresponding to the frequency of the acoustic waves generated by the photoacoustic effect, and thereby to the frequency at which the energy pulses are applied to the body; controlling the pulse source to change the frequency at which the energy pulses are applied to the body, and thereby the frequency of the acoustic waves, such that the detector detects a whole integer number of wavelengths in the acoustic channel irrespective of variations in the target substance concentration within the body; and utilizing a measurement of the frequency, or change in frequency, of the pulses to produce a measurement of the concentration, or change in concentration, of the target substance.

The "photoacoustic effect" utilized in the above method is well known and has long been used for non–invasively producing various types of measurements, e.g. temperature, pressure, composition, etc. It has also been proposed for use in non–invasively monitoring blood glucose levels, as described for example in US Patents 5,348,002, 5,348,003, 5,941,821, 6,833,540, and 6,846,288 Insofar as we are aware, however, a method utilizing this effect has not yet been implemented in a commercially–available device or in a device which has obtained FDA approval.

As will be described more particularly below, the present invention utilizes the "photoacoustic effect", together with the method, herein referred to as the Frequency–Change by Wavelength–Control (or FCWC) method described below and in the above–cited US Patent 6,621,278 and PCT Applications, for producing a glucose monitoring device capable of achieving high reliability without a need for frequent recalibration as compared to other known methods.

When the FCWC method is used in this aspect of the present invention, the energy wave transmitted through the transmission channel is the acoustic wave generated by the "photoacoustic effect"; and the medium of the channel is the body containing the target substance to be monitored, e.g. glucose in a patient's blood.

Embodiments of the present invention are described below which utilize the FCWC (Frequency–Change by Wavelength–Control) method described in the above–cited US Patent 6,621,278, to produce a precise measurement of the transit time of an acoustic wave through a transmission channel, and thereby of the concentration of the target substance being monitored to the extent that it changes this transit time by a change in the transit velocity and/or the transit distance. This aspect of the present invention utilizes the selective absorption of energy by the target substance, and particularly the "photoacoustic effect", for generating the acoustic waves used in the FCWC method. Accordingly, the present invention enables changes in glucose concentration to be measured with a high degree of accuracy, reliability and repeatability.

The invention, however, can also be implemented by using the FCWC method without the "photoacoustic effect", in order to measure the concentration of the glucose (or other target substance) according to the heat generated by the target substance, since

such generated heat also changes the transit time of an acoustic wave through an acoustic channel.

According to another aspect of the present invention, therefore, there is a provided a method of non–invasively measuring the concentration of a target substance within a body, comprising: transmitting acoustic waves through an acoustic wave transmission channel in the body to a detector at the opposite end of the acoustic wave transmission channel; applying to the body in the acoustic wave transmission channel energy highly absorbable by the target substance, as compared to other substances, to heat the portion of the body within the acoustic wave transmission channel according to the concentration of the target substance in the body; detecting the acoustic waves in the transmission channel to output an electrical signal having a frequency corresponding the frequency of the acoustic waves transmitted through the channel by the acoustic wave transmitter; controlling the acoustic wave transmitter to change the frequency thereof such that the detector detects a whole integer number of wavelengths irrespective of variations in the target substance concentration with the body; and utilizing the frequency of the detector output signal to produce a measurement of the target substance concentration. The magnitude of the detector output signal may also be used in producing the measurement of the target substance concentration.

An advantage of this aspect of the present invention is that it enables the FCWC method to be used in two independent manners for measuring the concentration of the target substance. Thus, it uses the selective heating by the target substance to produce, by the "photoacoustic effect", the acoustic waves used in the FCWC method. It also enables the increase in temperature produced by the selective heating to be precisely measured by the FCWC method to provide a measurement of the glucose concentration. In both cases, the FCWC method enables precisely measuring the change in transit time of the acoustic wave, and thereby any condition such as the change in temperature and/or composition, affecting the transit velocity of the acoustic wave. Thus, both techniques can be used in any particular monitoring operation, in order to improve the accuracy and reliability of the final result by executing one technique to extract data from the monitored site useful to determine concentration by the other techniques, or to corroborate the results produced by the other technique.

The present invention also enables a number of acoustic channels to be established through the monitored region for extracting therefrom various types of information which can be used to reduce the extraneous influences, and thereby to provide a more accurate measurement of the concentration of the target substance within the body.

According to another aspect of the present invention, therefore, there is provided a method of non–invasively measuring the concentration, or change in concentration, of a target substance within a body, comprising: transmitting acoustic waves through at least two separate acoustic channels in the body; applying to one of the channels energy which is selectively absorbable by the target substance to thereby heat the respective channel according to the concentration of the target substance therein; and measuring the difference in temperature between that in the one channel with respect to that in the other channel, to thereby provide a measure of the concentration, or change in concentration, of the target substance in the body.

According to still further aspects, the invention also provides apparatus for monitoring a condition, particularly for non–invasively measuring the concentration, or change in the concentration, of a target substance within a body according to the above methods.

In the described preferred embodiments, the pulse source is a laser having a wavelength selectively absorbable by the target substance; and the target substance is a constituent of the blood of a person, particularly the glucose in the person's blood. It will be appreciated, however, that the invention can use other pulse sources and can be used for determining the concentration, or change in concentration, of other target substances within other bodies.

Further features and advantages of the invention will be apparent from the description below.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is herein described, by way of example only, with reference to the accompanying drawings, wherein:

Fig. 1 is a block diagram illustrating one form of system constructed in accordance with the above–cited U.S. Patent 6,621,278 for precisely monitoring various

conditions having a known relation to, or influence on, the transit times of energy waves through a transmission channel;

Fig. 2 is a block diagram illustrating the system of Fig. 1 but modified to receive the cyclically–repeating energy wave directly, rather than the echoes thereof;

Fig. 3 is a block diagram illustrating the system of Fig. 1 applied with respect to an amplitude–modulated electromagnetic carrier wave in accordance with the present invention;

Figs. 4a–4d illustrate a series of waveforms helpful in understanding the operation of the system of Fig. 3;

Fig. 5 is a diagram illustrating how the modulation frequency (MHz) varies with the distance (m) in the system of Fig. 3;

Fig. 6 is a diagram illustrating a measuring system constructed in accordance with one aspect of the present invention utilizing a phase–locked loop circuit for continuously changing the frequency of the transmitter according to changes in the monitored condition; and

Figs. 7–12 are diagrams illustrating the invention implemented in various methods for monitoring blood glucose levels in a non–invasive manner.

THE BASIC FCWC METHOD

Fig. 1 is a block diagram illustrating the basic FCWC (Frequency–Change by Wavelength–Control) measuring method of the above–cited US Patent 6,621,278 and PCT Applications. The illustrated system is an echo system in which the distance to target T is measured by measuring the transit time taken by a cyclically–repeating energy wave transmitted at point A towards the target T until its echo is received at point B. The distance ATB thus constitutes the transmission channel between locations A and B.

The system illustrated in Fig. 1 thus includes a transmitter 2 at location A for transmitting the cyclically–repeating energy wave towards target T, and a receiver 3 at location B for receiving the echo of the cyclically–repeating energy wave after reflection from target T. Initially, the energy wave is continuously transmitted from an oscillator 4 under the control of a switch 5 until the echoes are received by receiver 3; once the echoes are received, switch 5 is opened so that the received echo signals are then used for

controlling the frequency of transmission of the cyclically–repeating energy wave by transmitter 2.

As shown in Fig. 1, the signals received by receiver 3 are fed to a comparator 6 via its input 6a. Comparator 6 includes a second input 6b connected to a predetermined bias so as to detect a predetermined fiducial or reference point in the received signal. In the example illustrated in Fig. 1, this predetermined fiducial point is the "zero" cross–over point of the received signal, and therefore input 6b is at a zero–bias. Other reference points could be used as the fiducial point, such as the maximum or minimum peak of the received signals.

The output of comparator 6 is fed to an amplifier or monostable oscillator 7 which is triggered to produce an output wave or signal for each fiducial point (zero cross–over point) in the signals received by the receiver 3. The signals from amplifier 7 are fed via an OR–gate 8 to the transmitter 2. OR–gate 8 also receives the output from oscillator 4 when switch 5 is closed.

Switch 5 is opened when the transmitter 2 receives a continuous stream of signals from amplifier 7 via OR–gate 8. When switch 5 is opened, transmitter 2 will thus transmit at a frequency determined by the fiducial points in the reflected signals received by receiver 3 and detected by comparator 6 to control amplifier 7. Accordingly the frequency of transmission by transmitter 2 will be such that the number of waves of the cyclically–repeating energy wave transmitted from location A and received in location B, i.e., in the loop including the transmission channel ATB, will be a whole integer.

It will thus be seen that while the frequency of the transmitter 2 will change with a change in the distance to the target point T, the number of wavelengths (λ) in the signal transmitted through the loop including the transmission channel ATB, from the transmitter 2 to the target T and reflected back to the receiver 3, will remain a whole integer. This is because the transmitter 2 transmissions are controlled by the fiducial points (zero cross–over points) of the signals received by receiver 3. This change in frequency by the transmitter 2, while maintaining the number of waves in the loop of the transmission channel ATB as a whole integer, enables a precise determination to be made of the distance ATB, and thereby of the distance to the target point T. Thus, as known:

$$F = C/\lambda$$

Where: F and C are the frequency and velocity, respectively, of the cyclically–repeating energy wave in the respective medium; and λ_L is the wavelength. For example, if the energy wave is an acoustic wave, and the medium is air under normal temperatures and pressures, C=340,000 mm/sec. Accordingly, if F=34 KHz, then λ–10mm.

Assuming the initial transmit path of transmission channel ATB (Fig. 1) is 100 mm, it will be seen that the number of wavelengths in the loop of this channel will be 10.

Now assuming that the transit distance of transmission channel ATB is increased by 1 mm, i.e., from 100 mm to 101 mm. While this transit distance is now increased from 100 mm to 101 mm, the transit time will also be increased. However, since the frequency of transmitter 2 is controlled by the fiducial point of the signals received by receiver 3, the transmitter 2 will still produce the same number of waves during this increased transit time, and therefore the waves will be slightly increased in length. Thus, the increased wavelength will be 101/10=10.1 mm. The frequency of transmitter 2 will therefore be changed from 34 KHz to 340,000/10.1=33,663 KHz.

The frequency will thus be decreased by 337 Hz when the distance is increased by 1 mm. Such a frequency change can be easily measured. If the distance is changed by 0.001 mm (rather than 1 mm), the frequency change will be 0.337 Hz, which would be extremely difficult, if possible at all, to measure in a practical manner. However, such a small frequency change can be easily measured in the system illustrated in Fig. 1 by including a summing circuit which continuously sums the measured frequency changes over a predetermined time, e.g., 100, 1,000, 10,000, or more cycles, and produces periodic read outs of the summed changes.

Thus, the zero cross–over points detected in comparator 6, which are used for controlling the frequency of the transmitter 2, are also fed to a counter 10 to be counted "N" times, and the output is fed to another counter 11 controlled by a clock 12. Counter 11 produces an output to a microprocessor 13 which performs the computations according to the parameter to be detected or measured, and a display 14 which displays the output of the microprocessor.

It will thus be seen that the system illustrated in Fig. 1 may be used for precisely measuring not only distance, but any other parameter having a known relation to the transit time of movement of the energy wave through the medium. It will also be seen

that the medium could be a liquid, a solid, or a gas; and that the energy wave could be an electromagnetic wave, an acoustic wave, etc. Since the measurement is done digitally, it is not subject to the limitations of accuracy, sensitivity and repeatability characteristic of analogue measurements. The measurement may be changes in the parameter during the measurement period, or the absolute value of the parameter at any instant during the measurement period.

Fig. 2 illustrates a modification in the system of Fig. 1, wherein the acoustic transmitter 22 transmits directly to the receiver 23, rather than by reflection, so that the transit distance of the transmission channel, and therefore the parameter measured by the control and measuring system 24, will be the actual line–of–sight distance between the transmitter and receiver.

Fig. 3 is a block diagram illustrating the invention implemented with respect to a method and apparatus utilizing an amplitude–modulated electromagnetic carrier waves, e.g., for measuring distance from an object. Such a system using very high carrier frequencies enables the use of compact, narrow, beam antennas or optical systems for transmission and reception.

Thus, in the system of Fig. 3, the transmitter includes a generator 70 for generating a cyclically–repeating electromagnetic carrier wave, and a modulator 71 for amplitude–modulating the carrier wave by a cyclically–repeating electromagnetic modulating wave. The modulated carrier wave is transmitted by the transmitter 72 towards the object 73 whose distance is being measured.

The modulated carrier wave, after being reflected by the object 73, is received by a receiver 74 and demodulated by a demodulator 75 separating the modulating wave from the received wave. In the illustrated system, there is further included a delay device 76, such as an acoustic delay line, for producing a phase shift of up to 360° in the separated modulating signal, before that signal is processed by the processor 77, in the manner described above, for detecting fiducial point of the received modulating signal and utilizing it for changing the frequency of the modulator 71 such that the number of modulating waves in the loop of the transmission channel is a whole integer.

Thus, the system illustrated in Fig. 3 provides feedback of the modulation frequency. The value of the modulation frequency will be set automatically so as to produce a phase shift in the feed–back loop of up to 360°. Thus:

$$fm = \frac{P}{\frac{2d}{c} + \frac{L}{v_S}}$$

where: fm – modulation frequency,

p – integer number,

d – distance to obstacle,

c – light velocity,

L – length of delay line,

V_S – sound velocity in delay line.

The provision of the acoustic delay line 76, which is optional, adds an artificial distance to the measurement, e.g., when a relatively high frequency is used and thereby a relatively small wave length is involved, or when otherwise there is a relatively short transit distance between the transmitter and the receiver.

It will be appreciated that the carrier wave generator 70, and also the modulator 71, could operate at the radio frequency, infrared, or optical bands of the electromagnetic spectrum. For example, the generator 70 could be in the GHz range, and the modulator 71 could be in the MHz range. The delay line 76 could be an acoustic delay line. In this example, if the integer number (p) is equal to 5, the length of the delay line (L) would be 5 mm, and the sound velocity in the delay line (v_S) would be 5,000 m/sec.

Fig. 4a illustrates the modulated carrier wave transmitted by transmitter 72, after having been amplitude–modulated by the signal from modulator 71 (point A), and Fig. 4b illustrates the modulated carrier wave outputted (point B) from the receiver 74, wherein it will be seen that the received wave has been phase shifted because of the change in distance of the object from the transmitter and receiver. Fig. 4c illustrates the demodulated wave (point C); and Fig. 4d illustrates the de–modulated wave (point D) after having been phase shifted by the delay line 76.

Fig. 4c also illustrates three examples of the predetermined fiducial point in the received signal, namely the "zero" cross–over point indicated by line a —— a, the maximum peak indicated by line b —— b; and minimum peak indicated by line c —— c, which may be used to change the frequency of the modulated wave such that the number of received de–modulated waves will be a whole integer.

Fig. 5 illustrates an example of the manner in which the modulation frequency (MHz) varies with the distance (m).

THE PHASE–LOCKED LOOP

Fig. 6 illustrates a system similar to that of Fig. 1, but based on a phase–locked loop for continuously changing the frequency of the transmitter according to changes in the monitored condition while maintaining the number of waves in the transmission channel loop as a whole integer.

In Fig. 6, the transmission channel is generally designated 100. It includes a transmitter 101 at one end, and a receiver 102 at the opposite end. The illustrated system further includes a phase–locked loop (PLL) 103 having an input 103a from the receiver 102 and an output 103b to the transmitter 101 of the transmission channel 100. Thus, PLL 103 includes a VCO (voltage–controlled oscillator) 104 which drives transmitter 101 of the transmission channel 100, and a phase detector 105 having one input from VCO 104, and a second input from receiver 102 of the transmission channel 100. Phase detector 105 thus produces an output corresponding to the difference in phases between the two inputs. The output of phase detector 105, after passing through a low–pass filter 106, is used to control the VCO 104 which drives transmitter such that the number of waves in the loop of the transmission channel 100 is and remains a whole integer.

As described above, the cyclically–repeating energy wave in transmission channel 100 may be an EMF wave, a sonic wave, or a modulated carrier wave; the transmission channel itself may be a gas, liquid or solid; and the monitored condition may influence the transit velocity and/or the transit distance of the cyclically–repeating energy wave through the transmission channel. Thus, any one of those conditions will influence the transit time of the energy wave through the transmission channel. The phase difference detected by phase detector 105 will correspond to the change in the transit time of the

energy wave through the transmission channel 100, and thereby to the changes in the monitored condition which influence this transit time.

The phase shift measured by phase detector 104 can be computed as follows:

$$\Delta\Theta = 2\pi\frac{L}{\lambda} = 2\pi\frac{L\cdot f}{c} = 2\pi\cdot t\cdot f\,[rad]$$

where: Θ – phase shift, rad,

L – distance between Transmitter and Receiver, m,

λ – length of energy wave in Medium, m,

f – frequency of VCO Hz,

c – velocity of energy propagation in Medium, m/sec,

t – transit time in medium, sec.

This phase shift appears as a voltage U on the output of the low–pass filter 104, as follows:

$$U = K_{PD}\cdot\Delta\Theta$$

where K_{PD} – transform function coefficient of the phase detector.

The frequency of VCO 104 is controlled by the output voltage U applied as a negative feed back to the VCO, as follows:

$$f = f_0(1 - K_{VCO}\cdot U)$$

where K_{VCO} – transform function coefficient of VCO.

Thus, an increase in the transit time results in a decrease of VCO frequency, and vice versa. Combining all equations

$$f = \frac{f_0}{1 + K_{PD} \cdot K_{VCO} \cdot 2\pi \cdot f_0 \cdot t}$$

It will be seen that the frequency of VCO 104 varies with, and is stabilized on, a value that depends on the transit time of the energy wave through the transmission channel 100. Since this transit time varies in a known manner with the condition being monitored, as noted above, the output of VCO 104 provides an indication of the monitored condition. The output of VCO 104 may therefore be displayed in a display device 107, and may also be stored, further processed, and/or used for controlling operation of another device, e.g., an alarm, etc.

NON–INVASIVE GLUCOSE MONITORING (FIGS. 7–12)

The apparatus illustrated in Fig. 7 includes a measuring circuit as described above with respect to Figs. 1–6 for non–invasively monitoring changes in the concentration of a target substance TS in the blood flowing through a monitored site 202 of a person. As indicated earlier, the method described is particularly useful for monitoring changes in the concentration of glucose in blood. Therefore the target substance TS is hereinafter referred to as glucose, but it will be appreciated that the invention could also be used for monitoring other target substances in other bodies, such as other constituents of blood, or constituents of urine, constituents of other biological fluids or other types of fluids, e.g., industrial fluids, or constituents of other bodies, i.e., solids and gases as well as liquids.

The apparatus illustrated in Fig. 7 includes a laser 203 which applies laser pulses via an optical fiber 204 to a selected region of the monitored site 202. Laser 203 may include a single laser, or a combination of lasers, having a wavelength or combination of wavelengths selectively absorbable by the glucose TS within the blood flowing through monitored site 202, as compared to other substances in the region exposed to the laser energy. As a result, the absorption of the laser energy by the glucose is effective to heat the respective region according to the glucose concentration in the blood. This absorption of the laser energy by the glucose generates, by the "photoacoustic effect", a series of acoustic waves, shown at 205 in Fig. 7, which are propagated through an acoustic channel 206 at a frequency corresponding to that at which the laser is pulsed. The acoustic waves so generated in channel 206 by the glucose TS are detected by an

acoustic detector 207 in contact with the external surface of the skin at the monitored site. For this purpose, acoustic detector 207 may be formed with a central opening to accommodate optical fiber 204 from the laser.

The frequency of activation of laser 203, and thereby the frequency of generation of the acoustic waves 205 by the photoacoustic effect, is controlled by detector 207 via a control lines 208 and 209, and a control and measuring system, generally designated 210. System 210 controls laser 203 in accordance with the above–described FCWC (Frequency–Change by Wavelength–Control) method, to change the frequency of application of the laser energy pulses, and thereby the frequency of the acoustic waves 205 through channel 206, such that the detector detects a whole integer number of wavelengths in channel 206 irrespective of the concentration of the glucose TS. Thus, the frequency of the laser pulses is changed by, and according to, changes in the concentration of glucose at the monitored site 202, so that the frequency change represents a measure of the glucose concentration change.

As shown in Fig. 7, the measurements produced by system 210 may be outputted to the following output units: a display unit 210a, such as a display in a wrist–worn monitoring device; an alarm unit 210b, such as a sounder or vibrator actuated to alert the person of an alarm condition; and/or a control device 210c, such as an automatic control for an insulin–delivery pump.

Fig. 8 more particularly illustrates the control and measuring system 210 of Fig. 7 for controlling the frequency of activation of laser 203, and thereby the generation of the acoustic waves 205 detected by detector 207, for maintaining the number of wavelengths of the acoustic waves as whole integer within channel 206 irrespective of the concentration of the glucose TS.

Initially, laser 203 is activated via line 209 by an oscillator 211 under the control of a switch 212 until the acoustic waves 205 are received by detector 207. Once these waves are received, switch 212 is opened, so that the received waves are thereafter used for controlling the activation of laser 203, and thereby the generation by the photoacoustic effect of the acoustic waves 205.

As shown in Fig. 8, the output of detector 207 is fed via line 208 to input 213a of a comparator 213. Comparator 213 includes a second input 213b connected to a

predetermined bias so as to detect a predetermined fiducial or reference point in the received signal. In the example illustrated in Fig. 8, this predetermined fiducial point is the "zero" crossover point of the signal outputted from detector 207; hence, input 213b is at a zero bias. However, other reference points could be used as the fiducial point, such as the maximum peaks, the minimum peaks, or the leading edges of the output signal from detector 207.

The output of comparator 213 is fed to a monostable oscillator 214 which is triggered to produce an amplified output signal at each fiducial point in the output signal from detector 207. The signals from monostableoscillator 214 are fed via an OR–gate 215 to control line 209 controlling the activation of laser 203.

It will thus be seen that laser 203 is activated at a frequency such that the photoacoustic waves 205, generated in channel 206 by the absorption of its energy by the targetted glucose TS, is a while integer. The changes in frequency of activation of laser 203, to maintain the number of waves 205 in channel 206 as a whole integer, thus represent a precise measurement of the changes in transit time of the waves 205 from the targetted glucose TS to the detector 207 resulting from the changes in the concentration of the glucose.

The precise measurement of the transit time of the glucose–generated acoustic waves to the detector 207 thus enables a precise measurement to be made of any parameter or condition affecting that transit time. The transit time depends on the transit velocity and the transit distance. Where the transit distance is known or determinable, the measured transit time will be a measure of the transit velocity, and thereby a measure of any factors, such as the heat generated by the glucose, on the transit velocity. Since the heat generated corresponds to the concentration of the glucose, the measured transit time will thus be a measure of the concentration of the glucose at the monitored site.

In addition to heat, other factors, such as changes in composition other than in the glucose concentration, may also affect the transit time of the acoustic wave through channel 6, but such influences for the large part can be determined beforehand or independently, in order to compensate for their influences on the measurements made.

Fig. 8 also illustrates a circuit for accumulating small changes in frequency, over a large time interval as also described in the above–cited US Patent 6,621,278. Thus, as

shown in Fig. 8, the signals outputted from comparator 213, used for controlling the frequency of activation of laser 203, are also fed to a counter 216 to be counted "N" times, and the output is fed to another counter 217 controlled by a clock 218. Counter 217 produces an output to a microprocessor 219 which performs the computations according to the parameter or condition to be measured, in this case the concentration of the targetted glucose TS at the monitored site. Microprocessor 219 produces the outputs to the display unit 210a, alarm unit 210b, and/or control unit 210c.

Further details of the construction, use and other possible applications of the control and measuring system 210 illustrated in Fig. 8 are set forth in the above–cited US Patent No. 6,621,278.

Fig. 9 illustrates a further embodiment of the invention also utilizing acoustic waves generated by the photoacoustic effect. This embodiment provides a number of acoustic channels each of which may be used for extracting various types of information from the monitored site to enable a more accurate determination to be made of the concentration of the targetted glucose. Whereas in the embodiment illustrated in Figs. 7 and 8 the monitored site requires access only from one side, (e.g., such as the person's wrist or fingertip), the embodiment illustrated in Fig. 9 utilizes a monitored site providing access from both sides, such as an ear lobe, finger web, or the like. For purposes of example, the person's ear lobe is used as the monitored site in Fig. 9.

The apparatus illustrated in Fig. 9 includes a sensor assembly, generally designated 220, for application to the ear lobe EL of the person. Sensor assembly 220 includes two plates 221, 222 slidably mounted on a holder 223, for engaging the opposite surfaces of the ear lobe EL. The two plates 221, 222 are movable within a channel 224 formed in holder 223 so as to maintain the two plates in exact parallel relationship to each other when engaging the opposite surfaces of the ear lobe.

The inner surface of each of plate 221, 222 carries three vertically–spaced acoustic transducers 231, 232, 233, and 241, 242, 243 respectively, aligned with each other when the sensor assembly 220 is mounted to the person's ear lobe. Thus, as shown in Fig. 9, transducers 231 and 241 define a first pair aligned with an intermediate region of the ear lobe; transducers 232 and 242 define a second pair aligned with a lower region of the ear lobe; and transducers 233 and 243 define a third pair aligned with each other in

the space below the ear lobe. The distance between the transducers in each of the pairs is equal and is either known or determinable, as will be described below.

Plate 221 of sensor assembly 220 also carries a laser 250 on its outer surface in alignment with acoustic transducer 231 on the inner surface of the plate. Transducer 231 is formed with a central opening to accommodate an optical fiber 251 extending from laser 250 to the inner face of plate 221 to be in contact with the outer surface of ear lobe EL.

Laser 250, and the three pairs of acoustic transducers 231–233 and 241–243, respectively, are connected to a control and measuring system 260. System 260 corresponds to the control and measuring system 210 illustrated in Figs. 7 and 8, but modified to accommodate three acoustic channels, rather than the one illustrated in Figs. 7 and 8.

Fig. 9 illustrates target substance TS (e.g., glucose), whose concentration is to be monitored, in alignment with optical fiber 251 from laser 250, acoustic transducer 231 on one side, and acoustic transducer 241 on the opposite site. Thus, when laser 250 is activated as described above with respect to Figs. 7 and 8, the glucose TS generates a series of acoustic waves by the photoacoustic effect. The so–produced acoustic waves propagate outwardly in all directions, including the direction towards transducer 231, and the opposite direction towards transducer 241. Thus, a first acoustic wave channel AC_1 is established between the glucose TS serving as the generator or transmitter of the acoustic waves, and transducer 231 serving as the detector of the acoustic waves. Similarly, a second acoustic channel AC_2 is established between the glucose and detector 241 on the opposite side.

The illustrated sensor assembly 220 defines two further acoustic channels, namely a third channel AC_3 within a lower part of the ear lobe between the two transducers 232, 242; and a fourth channel AC_4 in the space (air) between the two transducers 233 and 243 below the ear lobe. It will also be seen that the length of acoustic channel AC_3 is equal to that of AC_4 and is also equal to the sum of the two acoustic channels AC_1 and AC_2.

Each of the above four acoustic channels AC_1–AC_4 is controlled by the control and measuring system 260 in the same manner as system 210 described above with respect to Figs. 7 and 8, to precisely determine the transit time of the acoustic waves in

the respective channel. As described above, the so–measured transit time is a measure of the transit velocity through the respective channel AC_1–AC_4, and therefore of any condition influencing the transit velocity. The transit time also depends on the transit distance in the respective channel, but as indicated above, the transit distance is either previously known according to the settings of the two plates 221, 222, or is precisely determinable as will be described below.

As indicated above, the transmitter in acoustic channel AC_1 is the targetted glucose TS generating the photoacoustic waves which are detected by acoustic detector 231. Since the transit time of a laser beam from laser 250 to the target substance TS is negligible when compared to the transit time of acoustic waves generated by the glucose, the frequency of activation of laser 250 would be controlled by detector 231, via the control and measuring system 260 in the manner described above with respect to Fig. 8, such that detector 231 detects a whole integer number of wavelengths irrespective of variations in the glucose concentration.

The frequency of activation of laser 250, and therefore the frequency of the output signal from detector 231, is thus a precise measurement of the transit time in channel AC_1. This frequency can be used to provide information as to the transit distance, i.e., the length of channel AC_1 between the target substance TS and its detector 231. It can also be used to provide information as to any conditions influencing the transit velocity of the generated acoustic waves through channel AC_1.

The magnitude of the output signal from detector 231 is also a measure of the concentration of the glucose in the monitored site. Since the magnitude measurement is an analog signal, it is inherently less accurate than the frequency–change digital signal produced by the FCWC method described above with respect to Fig. 8.

Nevertheless, since the magnitude of the output signal at detector 231 represents a measure of the glucose concentration at the transmitter end of channel AC_1, reduced by the transit distance to the detector 231 and by the acoustic impedance of the medium in channel AC_1, it can also provide information useful in determining the glucose concentration at the monitored site. Thus, the transit distance is determinable with high accuracy from the other information extractable from all the channels AC_1–AC_4 as will be described more particularly below. The acoustic impedance within the channel is

influenced not only by the composition of the medium (constituted of tissue plus blood, including the targetted glucose constituent), but also by the temperature of the medium of channel AC_1. As more particularly described below, the latter influences are also determinable by the information extractable from the monitored site by the activation of a selected combination of the channels AC_1–AC_4.

The transmitter in acoustic channel AC_2 is also the targetted glucose TS generating the photoacoustic waves, but in this channel such waves are detected by detector 241. This channel would be activated by the control and measuring system 260 as described above, except that in this case, detector 241 (rather than detector 231) controls the activation of laser 250 to produce a whole integer number of wavelengths within channel AC_2 irrespective of variations in the glucose concentration in that channel. It will therefore be seen that, as described above with respect to channel AC_1, the frequency of the output signal from detector 241 would be a measure of the transit time of the acoustic signal in channel AC_2 (and thereby transit distance and the factors influencing transit velocity in channel AC_2); and that the magnitude of the output signal from detector 241 would be a measure of the glucose concentration, diminished by the transit distance and the acoustic impedance of that channel.

As indicated above, detector 231 may be operated as an acoustic transmitter to generate acoustic waves propagated through both channels AC_1 and AC_2 to the detector 241. In such an operation, the acoustic waves would be generated by transducer 231, rather than by the photoacoustic effect described above; and the length of the respective channel would be the sum of the lengths of channels AC_1 plus AC_2. During this operation, detector 241 would control, via control and measuring system 260, transmitter transducer 231 to maintain a whole integer number of acoustic waves within the combined channel AC_1 plus AC_2.

Accordingly, during this combined–channel mode of operation of the illustrated apparatus, the frequency of the output signal from detector 241 would be a precise measurement of the transit time of the acoustic wave from transmitter 231 to detector 241, and thereby a measure of the transit distance and/or the transit velocity within this combined acoustic channel. The transit distance, during this operation, is the sum of the transit distances of channels AC_1 and AC_2 referred to in the above–described operations

for extracting information from these two channels when individually activated. The transit velocity, on the other hand, would depend on the factors, including the nature of the medium (tissue plus blood including its glucose constituent), and the temperature of the medium, influencing the transit velocity of the acoustic waves through this combination channel.

It is to be noted that this combination channel (AC_1 plus AC_2) can be selectively heated by the activation of laser 250. This mode of operation of the apparatus, therefore, permits laser 250 to be energized or not energized during a glucose monitoring operation. Thus, by activating laser 250 merely to heat the medium within the channel (and not to produce the above–described photoacoustic waves), the temperature of the medium within this combination channel will be raised according to the glucose concentration. Therefore, the magnitude of the output signal from detector 241 also provides useful information since it will be a measure of the glucose concentration diminished by the transit distance to the detector 241, and the factors influencing the acoustic impedance in this combination channel.

Accordingly, this combination channel (AC_1 plus AC_2) may be activated without energizing laser 250 to define a baseline or reference for comparison. This combination channel may also be activated while laser 250 is energized to apply a controlled or measured amount of energy to the medium within this combination channel. Such a two–stage activation of the combination channel thus enables the extraction of information from the monitored site useful in determining the heat influence on the transit time (represented by the frequency of the output signal from detector 241), or on the glucose concentration (represented by the magnitude of the signal output from detector 241), produced by the laser energy absorbed by the targetted glucose within this combination channel.

Acoustic channel AC_3 does not use the photoacousticly generated waves as the transmitter, as in channels AC_1 and AC_2, when individually activated, but rather utilizes acoustic transducer 232 as a transmitter for transmitting acoustic waves through channel AC_3 for reception by detector 242. Therefore, detector 242 would control, via system 260, the frequency of transducer 232 as described above to maintain the number of wavelengths in channel AC_3 as a whole integer. Since the transit distance of this channel

is known or can be determined as indicated above, channel AC_3 can also be used for extracting information from the monitored site as to conditions influencing the transit velocity or acoustic impedance of the acoustic waves through that channel. The combination channel AC_1 plus AC_2, however, provides the additional advantage of permitting a two–stage activation of that channel, one stage including heating by the laser, as described above.

Acoustic channel AC_4, defined by transducers 233 and 243, includes the space (air) below the ear lobe. It may therefore be used for providing reference information for determining the precise transit distances of the other three channels as described above, or for determining the influences on the transit times, the transit velocity, or the acoustic impedance imposed by the ear lobe to the acoustic waves transmitted therethrough via the other channels, as described above.

Acoustic channel AC_1 could be activated by utilizing detector 231 to control the frequency of activation of laser 250 in order to produce a whole integer number of photoacoustic waves in channel AC_1 by the photoacoustic effect as described above . In this case, the frequency of activation of the laser would be influenced by the transit distance (length of channel AC_1) and the transit velocity through channel AC_1. Thus, the frequency of the output signal from detector 231 would be a precise measurement of the transit time of the acoustic wave through channel AC_1. The magnitude of the output signal from detector 231 would be a measure of the amount of laser energy absorbed by the targetted glucose, and thereby a measure of the glucose concentration as diminished by the transit distance and acoustic impedance within channel AC_1.

With respect to the measured transit time as represented by the frequency of the output signal from detector 231, this transit time would depend on the transit distance and the transit velocity of the acoustic wave within channel AC_1.

The transit distance is the length of channel AC_1. This can be determined with extremely high accuracy from the other information extractable from the monitored site via the other channels, as described herein.

The transit velocity is influenced by the physical nature of the medium in channel AC_1 and also by the temperature of the medium in that channel. The medium is the portion of the ear lobe between transducers 231 and 241. It is constituted mainly of

tissue and blood containing the targetted glucose whose concentration is to be determined. Information regarding the influence of the targetted glucose, of the tissue, and of the temperature, on the transit velocity of the acoustic waves within channel AC_1 is extractable from the other channels by independently performed tests, such as to enable assessing the magnitude of these influences on the transit velocity, and thereby on the glucose concentration measurements.

Acoustic channel AC_2 could be similarly activated by using detector 241 for controlling laser 250. The frequency and magnitude of this output signal from detector 241 would provide similar information as in channel AC_1 with respect to the factors in influencing the transit velocity of the acoustic waves through that channel.

The combined channel (AC_1 plus AC_2) could also be independently activated, by using transducer 231 as a transmitter and transducer 241 as a detector, and controlling the activation of detector 231 by the output signal from detector 241. Laser 250 could be selectively operated to influence the transit velocity by the selective heating of the combined channel as described above. Such operation would also enable extracting from the monitored site information useful with the other information for determining the medium and/or heat influences on the transit velocity.

Channel AC_3 can be similarly activated for extracting useful information from the monitored site. Thus, by using transducer 242 as a detector for controlling transducer 232 used as a transmitter, the information obtainable from channel AC_3 would depend on the transit distance and transit velocity in that channel. Since the transit distance AC_3 is equal to the sum of the transit distances in the two channels AC_1 and AC_2, and since the transit velocity in channel AC_3 is influenced primarily by the ear lobe tissue and not by the heat generated by the targetted glucose upon activation of the laser 250, information as to these influences is also obtainable from channel AC_3. Such information can be used with the information obtainable when activating the other channels to assess the magnitude of these influences on the transit velocity, and thereby on the determination of the concentration of the glucose in the monitored site.

Acoustic channel AC_4, may also be activated to provide further useful information enabling a precise measurement of the length of channel AC_4 and thereby of the lengths of channel AC_1, AC_2 and AC_3. Channel AC_4 is not affected by the heat generated by

target substance TS or by the ear lobe tissue medium, influencing the transit velocity in the above–described channels AC_1–AC_3. Accordingly, the information obtainable from channel AC_4 could also be useful to assess the medium and/or heat influences on the transit velocity, and thereby to enable a more precise measurement of the glucose concentration to be made.

The apparatus illustrated in Fig. 9 also permits independent measurements to be made using the laser 250 merely as a heat source, rather than as a means for generating photoacoustic waves.

Thus, the FCWC (Frequency–Change by Wavelength–Control) method described above with respect to Fig. 8 (and more particularly described in the above–cited US Patent 6,621,278) can be used for producing a measurement of the concentration of the glucose (or other target substance) according to the amount of heat absorbed from the laser. In the apparatus illustrated in Fig. 9, this would be done in the above–described combination channel AC_1 plus AC_2 by activating laser 250 (e.g., at a measured rate and intensity so as not to damage the tissue) to transmit acoustic waves from transducer 231, acting as a transmitter, to detector 241. As described above, detector 241 would control the frequency of transmitter 231 to produce and maintain a whole integer number of wavelengths in the combination channel (AC_1 plus AC_2) between the transmitter 231 and detector 241.

The frequency of transmitter 231 would, therefore, depend on the transit distance and transit velocity between transmitter 231 and detector 241. The transit distance is known, or determinable as described above. The transit velocity varies with the heat generated by the glucose TS absorbing the laser energy. Since the heat so generated depends on the concentration of the glucose, the difference in frequency of transmitter 231 to maintain the number of wavelength as a whole integer in the combination channel AC_1 plus AC_2 (a) when this channel is activated with the activation of the laser, and (b) when this channel is activated without the activation of the laser, would be a measure of the heat generated within that channel by the glucose, and thereby a measure of the concentration of the glucose in the monitored site.

Such a measurement of the glucose concentration is not dependent on the photoacoustic effect. It therefore can be used alone for determining glucose

concentration. Alternatively, it can be used together with above–described method utilizing the photoacoustic effect in order to corroborate the results produced by that measurement, or to extract information from the monitored site useable to increase the reliability and repeatability of the measurements based on the photoacoustic effect.

It will further be seen that another independent measurement of the glucose concentration can be made using the laser merely to heat the monitored site by utilizing the magnitude, rather than the frequency, of the output signal from detector 241. In that case, the magnitude of the output signal would be a measure of the glucose concentration, reduced by the transit distance influence and the acoustic impedance influence to detector 231, as described above. This can be done by activating the combined channel AC_1 plus AC_2 (a) without activating the laser, and then (b) while activating the laser to introduce a measured amount of energy converted to heat by the glucose according to its concentration, and comparing the magnitude of the detector output for both cases. Such an independent measurement of the glucose concentration, although less precise than the measurement based on frequency change, could nevertheless be made to corroborate a frequency–change measurement, and/or to extract from the monitored site information useful in increasing the precision and repeatability of the measurement made by the frequency–change method..

Fig. 10 illustrates a modification in the sensor assembly 220 of Fig. 9, wherein transducers 232 and 242, defining acoustic channel AC_3 in Fig. 9, are omitted. In this case, similar information can be obtained as obtained from channel AC_3 in Fig. 8, by using transducer 231 as a transmitter, and transducer 241 as a receiver, to thereby produce the operation described above with respect to the combination channel AC_1 plus AC_2. In such an arrangement, the combination channel could be operated at one time while receiving laser energy, and at another time while not receiving laser energy, so as to provide a base line or reference for measuring the heat influence in the former operation.

In all other respects, the apparatus illustrated in Fig. 10 is constructed, and may be operated, in the same manner as described above with respect to Fig. 9, and therefore to facilitate understanding, the same numerals have been used with respect to corresponding elements.

Fig. 11 illustrates a further apparatus constructed in accordance with the present invention, similar to that of Fig. 7 in that the monitored site requires access only from one side, thereby permitting a person's wrist, fingertip, or the like, to be used as a monitoring site. The system illustrated Fig. 11 differs from that in Fig. 7 in that the Fig. 11 system provides not a single acoustic channel as in Fig. 7, but rather a plurality of acoustic channels, as described above with respect to Figs. 9 and 10, to enable various types of information to be extracted from the monitored site during a monitoring operation, such as to increase the reliability and repeatability of the glucose measurement, while reducing the need for frequent recalibration.

Thus, as shown in Fig. 11, the detector assembly, generally designated 270, includes three (or more) piezoelectric transducers 271, 272, 273, mounted in predetermined fixed positions on a mounting plate 274, configured for application to the monitoring site, e.g. a wrist of the person. Center transducer 272 is formed with an opening receiving an optical fiber 275 from a laser 276, such that the laser energy is supplied by pulses through transducer 272 to the target substance TS (e.g., glucose) whose concentration is being monitored. As described above, the absorption of the laser energy by the target substance TS generates heat according to the concentration of the glucose. This heat may be used to generate acoustic waves by the photoacoustic effect, which waves are propagated outwardly in all directions.

In one operation, the three transducers 271–273 may be used as detectors for detecting the so–generated acoustic waves. Thus, a separate acoustic channel is established between the targetted glucose TS and each of the three detectors 271–273. The illustrated apparatus further includes a control and measuring system 280, similar to system 210 (Figs. 7 and 10) or system 260 (Figs. 9 and 10) connected to the three detectors 271–273 and to laser 276.

Each of the detectors 271–273, which defines a separate acoustic channel with the targetted glucose TS, may control the laser 276, via control system 280, such that the frequency of the acoustic waves generated in the respective channel is a measure of the transit time of the acoustic wave in that channel. As described above, the transit time is dependent on the transit distance and the transit velocity in the respective channel. Since the locations of the three detectors 271–273 are known relative to each other, the transit

distance (e.g., the length of the respective channel) can easily be determined from the data extracted from the three channels of the monitored site. As also described above, the transit velocity in the respective channel is influenced by the nature of the medium (e.g., tissue plus blood including the glucose), and the temperature of the medium. By using three (or more) such channels as illustrated in Fig. 11, such influences can also be determined, or least closely approximated, from the information extracted from the monitored site.

In another operation, one transducer (e.g., 272) could be used as a transmitter of acoustic waves (instead of the targetted glucose by the photoacoustic effect) to the other transducer, and the laser could be used merely to selectively heat the respective acoustic channels. Thus, by selectively activating the two channels via the above–described FCWC method, with and without activating laser 276, information may be obtained useful in determining the influences of the heat and the channel medium on the transit velocity of the acoustic waves at the monitored site.

While Fig. 7 illustrates an embodiment of the invention wherein a single acoustic channel is created at a single monitoring site, and Figs. 9–11 illustrate embodiments wherein a plurality of acoustic channels are created at a single monitoring site, Fig. 12 illustrates a further embodiment wherein a plurality of acoustic channels are created at two (or more) monitoring sites.

The two monitoring sites in the embodiment of Fig. 12 are the two ear lobes of the person being tested. Presumably the glucose concentration, and the various influences involved in determining glucose concentration according to the above–described method, are sufficiently similar in the two ear lobes to enable extracting information from one site useful in the determination of the glucose concentration in the other site. If not, one ear lobe can be pre–calibrated with respect to the other.

For purposes of example, Fig. 12 illustrates two sensor assemblies, therein designated 220a, 220b, each constructed as sensor assembly 220 in Fig. 10; therefore, in order to facilitate understanding, corresponding elements are identified by the same reference numerals. Preferably, but not necessarily, both sensor assemblies include a laser 250, to enable operation of the respective sensor assembly according to any one of several possible modes. Thus, the arrangement illustrated in Fig. 12 enables a wide

variety of modes of operation to be selected for any particular case in order to extract information from both monitoring sites useful in determining the glucose concentration in the person's blood.

For example, one sensor assembly may be operated according to the above–described "photoacoustic mode", wherein the laser is used to produce acoustic waves by the photoacoustic effect, while the other sensor assembly is operated according to the above–described "heating mode", wherein the laser is used merely to heat the monitored site. Another option would be to activate the laser of one sensor assembly in order to generate heat by the selective absorption of the laser energy according to the glucose concentration at the respective site, while the laser in the other sensor assembly is not energized. Thus, the results of the test in the latter site could be used as a baseline or reference for the test results produced in the former site in assessing the influence of the heat absorbed by the glucose in the former site, which absorbs heat in accordance with its concentration.

Many of the other options described above with respect to a single site would also be available in the two–site arrangement of Fig. 12, in order to extract information from the two monitored sites which can be used to either corroborate the test results produced at one site, to increase the accuracy, reliability and repeatability of the test results, or to reduce the need for frequent recalibration of the apparatus.

As indicated above, various monitoring sites could be used. If an ear lobe is used for the monitoring site, the electrode assembly could be constructed as a separate unit for mounting to the ear lobe, whereas the control and display system could be in a separate unit wire–connected to the sensor unit. Another alternative would be to have the control and display unit incorporated in a wristband for mounting on the wrist of the person, and to have wireless communication with the sensor unit mounted on the person's ear lobe.

It will be appreciated that in all of the above–described embodiments, the laser wave length is selected according to the target substance of interest. Thus, if the target substance of interest is blood glucose, the laser wave length would be selected to have a frequency, or combination of frequencies, to generate the maximum level of acoustic waves by the photoacoustic effect in glucose, as described for example in the above–cited US patents. It will be further appreciated that excitation means other than lasers can be

used, e.g. microwaves, X–rays, ion–beams, etc, and that other target substances may be monitored, such as other blood constituents, urine constituents, constituents of other biological fluids, and constituents of industrial fluids, solid bodies, etc.

Therefore, while the invention has been described with respect to several preferred embodiments, it is to be expressly understood that these are set forth merely for purposes of example, and that many other variations, modifications and applications of the invention may be made.

WHAT IS CLAIMED IS:

1. A method of monitoring a condition having a known relation to, or influence on, the transit time of transmission of a cyclically–repeating energy wave moving through a transmission channel from a transmitter at one end to a receiver at the opposite end, comprising the following operations: (a) transmitting a cyclically–repeating energy wave through said transmission channel; (b) continuously changing the frequency of the transmission according to changes in the monitored condition while maintaining the number of waves in a loop including the transmission channel as a whole integer; and (c) utilizing the changes in frequency of the transmission to provide a continuous indication of the monitored condition; characterized in that operation (b) is performed by a phase–locked loop circuit having an input from said receiver, and an output controlling said transmitter.

2. The method according to Claim 1, wherein said phase–locked loop includes a phase detector, a low–pass filter, and a voltage–controlled oscillator; said voltage–controlled oscillator being connected to drive said transmitter and also to provide a first input to said phase detector; the output of said receiver being connected to said phase detector to provide a second input to said phase detector such that said phase detector produces an output corresponding to the difference in phases between said first and second inputs; said output of the phase detector, after passing through said low–pass filter, being utilized to control the voltage–controlled oscillator to drive said transmitter such that the number of waves in the loop of said transmission channel is a whole integer.

3. The method according to Claim 1, wherein said cyclically–repeating energy wave transmitted through said transmission channel is a modulating wave modulating a carrier wave; the frequency of the modulating wave being changed such that the number of modulating waves in the loop of said transmission channel is a whole integer.

4. The method according to Claim 1, wherein the phase of each cyclically–repeating energy wave received is shifted by a delay device up to 360° such that the number of such waves in the loop of said transmission channel is a whole integer.

5. A method of measuring the transit time of transmission of a cyclically–repeating energy wave moving through a transmission channel from a transmitter at one end to a receiver at the opposite end, comprising: continuously controlling the frequency

of the transmission such that the number of waves in a loop including the transmission channel is a whole integer; continuously measuring the frequency of the transmission; and utilizing the measured frequency of the transmission to provide a continuous indication of said transit time; characterized in that the frequency of the transmitter is continuously controlled by: connecting a voltage–controlled oscillator to drive said transmitter and also to provide a first input to a phase detector; utilizing the output of said receiver to provide a second input to said phase detector and to produce an output from said phase detector corresponding to the difference in phase between the first and second inputs; and utilizing said output of the phase detector to control the voltage–controlled oscillator to drive said transmitter such that the number of waves in the loop including said transmission channel is a whole integer.

6. The method according to Claim 5, wherein said phase–locked loop includes a phase detector, a low–pass filter, and a voltage–controlled oscillator; said voltage–controlled oscillator being connected to drive said transmitter and also to provide a first input to said phase detector; the output of said receiver being connected to said phase detector to provide a second input to said phase detector such that said phase detector produces an output corresponding to the difference in phases between said first and second inputs; said output of the phase detector, after passing through said low–pass filter, being utilized to control the voltage–controlled oscillator to drive said transmitter such that the number of waves in the loop of said transmission channel is a whole integer.

7. Apparatus for monitoring a condition having a known relation to, or influence on, the transit time of movement of an energy wave through a medium, comprising: a transmitter for transmitting a cyclically–repeating energy wave through a transmission channel in said medium; a receiver for receiving said cyclically–repeating energy wave transmitted through said transmission channel; and a processor for continuously changing the frequency of transmission of the cyclically–repeating energy wave through said transmission channel in accordance with changes in the monitored condition while maintaining the number of waves in a loop including said transmission channel as a whole integer, and for utilizing the change in frequency to produce a measurement of said monitored condition; characterized in that said processor includes a phase–lock loop circuit connected between said receiver and transmitter of said

transmission channel to continuously control the transmitter in response to an input from the receiver to change the number of waves in the loop of the transmission channel such as to be a whole integer.

8. The apparatus according to Claim 7, wherein said phase–locked loop includes a phase detector, a low–pass filter, and a voltage–controlled oscillator; said voltage–controlled oscillator being connected to drive said transmitter and also to provide a first input to said phase detector; the output of said receiver being connected to said phase detector to provide a second input to said phase detector such that said phase detector produces an output corresponding to the difference in phases between said first and second inputs; said output of the phase detector, after passing through said low–pass filter, being utilized to control the voltage–controlled oscillator to drive said transmitter such that the number of waves in the loop of said transmission channel is a whole integer.

9. The apparatus according to Claim 7, wherein:

said transmitter includes a generator for generating a carrier wave, and a modulator for modulating said carrier wave by a modulating wave in accordance with the monitored condition, which modulated carrier wave is transmitted by said transmitter and received by said receiver;

said receiver includes a demodulator for separating said modulating wave from the received wave;

and said processor continuously changes the frequency of the modulating wave at the transmitter such that the number of modulating waves in the loop of said transmission channel is a whole integer.

10. The apparatus according to Claim 7, wherein the apparatus further includes a delay device for producing a phase shift of up to 360° in the received wave before utilized by the processor for changing the frequency of the transmitter such that the number of waves in the loop of said transmission channel is a whole integer.

11. The apparatus according to Claim 7, wherein said cyclically–repeating energy wave transmitted through said transmission channel is an acoustic wave generated by the impingement of an electromagnetic beam against a target.

12. The apparatus according to Claim 11, wherein said electromagnetic beam is a laser beam which generates said acoustic wave by the photoacoustic effect when impinging said target.

13. The apparatus according to Claim 11, wherein said electromagnetic beam is selective with respect to a particular substance in the target such that the monitored condition is a parameter of said substance in the target.

14. The apparatus according to Claim 11, wherein the monitored condition is the level of glucose in blood.

15. A method of non–invasively measuring concentration, or change in the concentration, of a target substance within a body, comprising the operations:

activating a pulse source to apply to said body a series of pulses of energy highly absorbable by said target substance, as compared to other substances, to heat said body and to generate therein, by the photoacoustic effect, a series of acoustic waves propagated through an acoustic channel in said body at a frequency corresponding to that at which said energy pulses are applied to the body;

detecting said acoustic waves to produce an electrical signal having a frequency corresponding to the frequency of said acoustic waves generated by the photoacoustic effect, and thereby to the frequency at which said energy pulses are applied to said body;

controlling said pulse source to change the frequency at which said energy pulses are applied to the body, and thereby the frequency of said acoustic waves, such that said detector detects a whole integer number of wavelengths in said acoustic channel irrespective of variations in the target substance concentration within said body;

and utilizing a measurement of the frequency, or change in frequency, of said pulses to produce a measurement of the concentration, or change in concentration, of said target substance.

16. The method according to Claim 15, wherein the magnitude, or change in magnitude, of said acoustic waves generated by the photoacoustic effect is also utilized in producing a measurement of the concentration, or change in concentration, of said target substance.

17. The method according to Claim 15, wherein said pulse source is a laser having a wavelength, or combination of wavelengths, selectively absorbable by said target substance.

18. The method according to Claim 15, wherein said target substance is a constituent of a body fluid of a person.

19. The method according to Claim 15, wherein said target substance is glucose in the blood of a person.

20. The method according to Claim 15, wherein said detector defines with said target substance a first acoustic channel between said target substance and said detector through which said acoustic waves generated by said photoacoustic effect are propagated, and a second acoustic channel between said target substance and a second detector through which said acoustic waves generated by said photoelectric effect are also propagated;

and wherein said method further comprises performing said controlling and utilizing operations also with respect to said pulse source and said second detector of said second acoustic channel.

21. The method according to Claim 20, wherein said detector in said first acoustic channel is a piezoelectric device which is also operated as a transmitter of acoustic waves through said first and second acoustic channels to said second detector of said second acoustic channel.

22. The method according to Claim 20, wherein said method further comprises:

providing a piezoelectric acoustic wave generator and a piezoelectric acoustic wave detector defining a third acoustic channel through said body of a length equal to the sum of the lengths of said first and second acoustic channels;

and performing said controlling and utilizing operations also with respect to said piezoelectric acoustic wave generator and acoustic wave detector of said third acoustic channel.

23. The method according to Claim 20, wherein said method further comprises:

providing a further piezoelectric acoustic wave generator and a further piezoelectric acoustic wave detector defining between them a further acoustic channel outside of said body and of a length equal that of said first and second acoustic channels;

and performing said controlling and utilizing operations also with respect to said further piezoelectric acoustic wave generator and detector of said further acoustic channel.

24. The method according to Claim 15, wherein said method further comprises:

providing a piezoelectric acoustic wave transmitter for generating and transmitting acoustic waves through said acoustic channel in said body to said detector;

activating said energy source to apply said energy pulses to heat the portion of said body in said acoustic channel according to the concentration of said target substance therein;

controlling said piezoelectric acoustic wave transmitter to change its frequency such that said detector detects a whole integer number of wavelengths in said acoustic channel irrespective of variations in the target substance concentration within said body;

and utilizing also the frequency, or change in frequency, of the detector output in producing a measurement of concentration, or the change in concentration, of said target substance.

25. The method according to Claim 24, wherein the method further comprises utilizing also the measurements of the detector output in producing a measurement of the concentration, or change in concentration, of said target substance.

26. A method of non–invasively measuring the concentration, or change in concentration, of a target substance within a body, comprising:

transmitting acoustic waves through an acoustic wave transmission channel in said body to a detector at the opposite end of said acoustic wave transmission channel;

applying to said body in said acoustic wave transmission channel, energy highly absorbable by said target substance, as compared to other substances, to heat the portion of said body within said acoustic wave transmission channel according to the concentration of said target substance in said body;

detecting said acoustic waves in said transmission channel to output an electrical signal having a frequency corresponding the frequency of said acoustic waves transmitted through said channel by said acoustic wave transmitter;

controlling said acoustic wave transmitter to change the frequency thereof such that the detector detects a whole integer number of wavelengths irrespective of variations in the target substance concentration with said body;

and utilizing the frequency of said detector output signal to produce a measurement of the concentration, or change in concentration, of said target substance.

27. The method according to Claim 26, wherein the magnitude, of said detector output signal is also utilized to produce a measurement of the concentration, or change in concentration, of said target substance.

28. The method according to Claim 26, wherein said pulse source is a laser having a wavelength selectively absorbable by said target substance.

29. The method according to Claim 26, wherein said target substance is a constituent of a body fluid of a person.

30. The method according to Claim 26, wherein said target substance is glucose in the blood of a person.

31. The method according to Claim 26, wherein said energy is selectively controlled so as to be supplied in the form of pulses such as to generate in said body, by the photoacoustic effect, a series of acoustic waves also propagated through said channel in the body but at a frequency corresponding to that at which the energy pulses are applied to the body;

and wherein said detector is selectively controlled to also detect said photoacousticly–generated acoustic waves, to control the energy source supplying said energy pulses to change the frequency of application of the energy pulses to the body, and thereby the frequency of said acoustic waves, such that the detector detects a whole integer number of wavelengths irrespective of variations in the target substance concentration within the body, and to utilize the frequency of said energy pulses in producing a measurement of the concentration, or change in concentration, of the target substance.

32. A method of non–invasively measuring the concentration, or change in concentration, of a target substance within a body, comprising:

transmitting acoustic waves through at least two separate acoustic channel in said body;

applying to one of said channels energy which is selectively absorbable by the target substance to thereby heat the respective channel according to the concentration of the target substance therein;

and measuring the difference in temperature between that in said one channel with respect to that in the other channel, to thereby provide a measure of the concentration, or change in concentration, of the target substance in the body.

33. The method according to Claim 32, wherein said two separate channels are in the same monitored site of said body.

34. The method according to Claim 32, wherein said two separate channels are in different monitored sites of said body.

35. The method according to Claim 32, wherein said difference in temperature is measured by measuring the transit time of an acoustic wave through each of said channels, and subtracting one transit time from the other.

36. The method according to Claim 35, wherein the transit time of an acoustic wave is measured in each of said channels by:

detecting each acoustic wave at the end of the respective channel;

controlling the frequency of transmission of acoustic wave into the respective channel such as to produce a whole integer number of waves in the respective channel;

and utilizing the changes in frequency in the respective channel to determine the transit time of the acoustic wave in the respective channel.

37. The method according to Claim 36, wherein the difference in the magnitudes of the acoustic waves at the end of the respective channel is also utilized in providing a measurement of the concentration, or change in concentration, of the target substance within the body.

38. The method according Claim 32, wherein said energy is applied to one of said channels in the form of pulses to generate said acoustic waves by the photoacoustic effect, as well as to heat the respective channel according to the concentration of the target substance therein.

39. The method according to Claim 32, wherein said acoustic waves transmitted through both said channels are generated by piezoelectric devices; and wherein said energy

is applied only to one of said channels to heat the respective channel according to the concentration of the target substance therein.

40. The method according to Claim 32, wherein said pulse source is a laser having a wavelength selectively absorbable by said target substance.

41. The method according to Claim 32, wherein said target substance is a constituent of a body fluid of a person.

42. The method according to Claim 32, wherein said target substance is glucose in the blood of a person.

43. Apparatus for non–invasively measuring changes in the concentration, or change in concentration, of a target substance within a body, comprising:

a pulse source for applying to said body a series of pulses of energy highly absorbable by said target substance, as compared to other substances, to heat said body and to generate therein, by the photoacoustic effect, a series of acoustic waves propagated through an acoustic channel in said body at a frequency corresponding to that at which said energy pulses are applied to the body;

a detector for detecting said acoustic waves to produce an electrical signal having a frequency corresponding to the frequency of said acoustic waves generated by the photoacoustic effect, and thereby to the frequency at which said energy pulses are applied to said body;

and a control and measuring system for controlling said pulse source to change the frequency at which said energy pulses are applied to the body, and thereby the frequency of said acoustic waves, such that said detector detects a whole integer number of wavelengths in said acoustic channel irrespective of variations in the target substance concentration within said body; and for utilizing a measurement of the frequency, or change in frequency, of said pulses to produce a measurement of the concentration, or change in concentration, of said target substance.

44. The apparatus according to Claim 43, wherein said control and measuring system also utilizes the magnitude, or change in magnitude, of said acoustic waves generated by the photoacoustic effect in producing a measurement of the concentration, or change in concentration, of said target substance.

45. The apparatus according to Claim 43, wherein said pulse source is a laser having a wavelength, or combination of wavelengths, selectively absorbable by said target substance.

46. The apparatus according to Claim 43, wherein said detector defines with said target substance a first acoustic channel between said target substance and said detector through which said acoustic waves generated by said photoacoustic effect are propagated, and a second acoustic channel between said target substance and a second detector through which said acoustic waves generated by said photoelectric effect are also propagated;

and wherein said control and measuring system performs said controlling and utilizing operations also with respect to said pulse source and said second detector of said second acoustic channel.

47. The apparatus according to Claim 46, wherein said detector in said first acoustic channel is a piezoelectric device which is also operated as a transmitter of acoustic waves through said first and second acoustic channels to said second detector of said second acoustic channel.

48. The apparatus according to Claim 32, wherein said apparatus further comprises:

a piezoelectric acoustic wave generator and a piezoelectric acoustic wave detector defining a third acoustic channel through said body of a length equal to the sum of the lengths of said first and second acoustic channels;

and wherein said control and measuring system performs said controlling and utilizing operations also with respect to said piezoelectric acoustic wave generator and acoustic wave detector of said third acoustic channel.

49. The apparatus according to Claim 46, wherein said apparatus further comprises:

a further piezoelectric acoustic wave generator and a further piezoelectric acoustic wave detector defining between them a further acoustic channel outside of said body and of a length equal that of said fist and second acoustic channels;

and wherein said control and measuring system performs said controlling and utilizing operations also with respect to said further piezoelectric acoustic wave generator and detector of said further acoustic channel.

50. The apparatus according to Claim 43, wherein said apparatus further comprises:

a piezoelectric acoustic wave transmitter for generating and transmitting acoustic waves through said acoustic channel in said body to said detector;

and wherein said control and measuring system activates said energy source to apply said energy pulses to heat the portion of said body in said acoustic channel according to the concentration of said target substance therein; controls said piezoelectric acoustic wave transmitter to change its frequency such that said detector detects a whole integer number of wavelengths in said acoustic channel irrespective of variations in the target substance concentration within said body; and utilizes also the frequency, or change in frequency, of the detector output in producing a measurement of the concentration, or change in concentration, of said target substance.

51. The apparatus according to Claim 50, wherein said control and measuring system utilizes also the magnitude, or change in magnitude, of the detector output in producing a measurement of the concentration, or change in concentration, of said target substance.

52. Apparatus for non–invasively measuring the concentration, or change in concentration, of a target substance within a body, comprising:

a transmitter for transmitting acoustic waves through an acoustic wave transmission channel in said body to a detector at the opposite end of said acoustic wave transmission channel;

an energy source for applying to said body in said acoustic wave transmission channel energy highly absorbable by said target substance, as compared to other substances, to heat the portion of said body within said acoustic wave transmission channel according to the concentration of said target substance in said body;

a detector for detecting said acoustic waves in said transmission channel to output an electrical signal having a frequency corresponding the frequency of said acoustic waves transmitted through said channel by said acoustic wave transmitter;

and a control and measuring system for controlling said acoustic wave transmitter to change the frequency thereof such that the detector detects a whole integer number of wavelengths irrespective of variations in the target substance concentration with said body; and for utilizing the frequency, or change in frequency, of said detector output signal to produce a measurement of concentration, or change in concentration, of said target substance.

53. The apparatus according to Claim 52, wherein said control and measuring system also utilizes the magnitude of said detector output signal to produce a measurement of said target substance concentration.

54. The apparatus according to Claim 52, wherein said pulse source is a laser having a wavelength selectively absorbable by said target substance.

55. The apparatus according to Claim 52, wherein said energy source is a pulse source selectively controlled so as to output pulses which generate in said body, by the photoacoustic effect, a series of acoustic waves also propagated through said channel in the body but at a frequency corresponding to that at which the energy pulses are applied to the body;

and wherein said control and measuring system selectively controls said detector to also detect said photoacousticly–generated acoustic waves; controls said pulse sources to change the frequency of application of the energy pulses to the body, and thereby the frequency of said acoustic waves, such that the detector detects a whole integer number of wavelengths irrespective of variations in the target substance concentration within the body; and utilizes the frequency of said energy pulses in producing a measurement of the target substance concentration.

56. Apparatus for non–invasively measuring the concentration of a target substance within a body, comprising:

a transmitter for transmitting acoustic waves through at least two separate acoustic channel in said body;

a source of energy for applying to one of said channels energy which is selectively absorbable by the target substance to thereby heat the respective channel according to the concentration of the target substance therein;

and a control and measuring system for measuring the difference in temperature between that in said one channel with respect to that in the other channel, to thereby provide a measure of the concentration of the target substance in the body.

57. The apparatus according to Claim 56, wherein said control and measuring system measures said difference in temperature by measuring the transit time of an acoustic wave through each of said channels, and subtracting one transit time from the other.

58. The apparatus according to Claim 57, wherein said control and measuring system measures the transit time of an acoustic wave in each of said channels by:

detecting each acoustic wave at the end of the respective channel;

controlling the frequency of transmission of acoustic wave into the respective channel such as to produce a whole integer number of waves in the respective channel;

and utilizing the frequency, or change in frequency, in the respective channel to determine the transit time of the acoustic wave in the respective channel.

59. The apparatus according to Claim 58, wherein said control and measuring system also utilizes the differences in the magnitudes of the acoustic waves at the end of the respective channel in providing a measurement of the concentration, or change in concentration, of the target substance within the body.

60. The apparatus according Claim 56, wherein said source of energy is a pulse source which supplies pulses to one of said channels to generate said acoustic waves by the photoacoustic effect, as well as to heat the respective channel according to the concentration of the target substance therein.

61. The apparatus according to Claim 56, wherein said acoustic waves transmitted through both said channels are generated by piezoelectric devices; and wherein said energy is applied only to one of said channels to heat the respective channel according to the concentration of the target substance therein.

62. The apparatus according to Claim 56, wherein said pulse source is a laser having a wavelength selectively absorbable by said target substance.

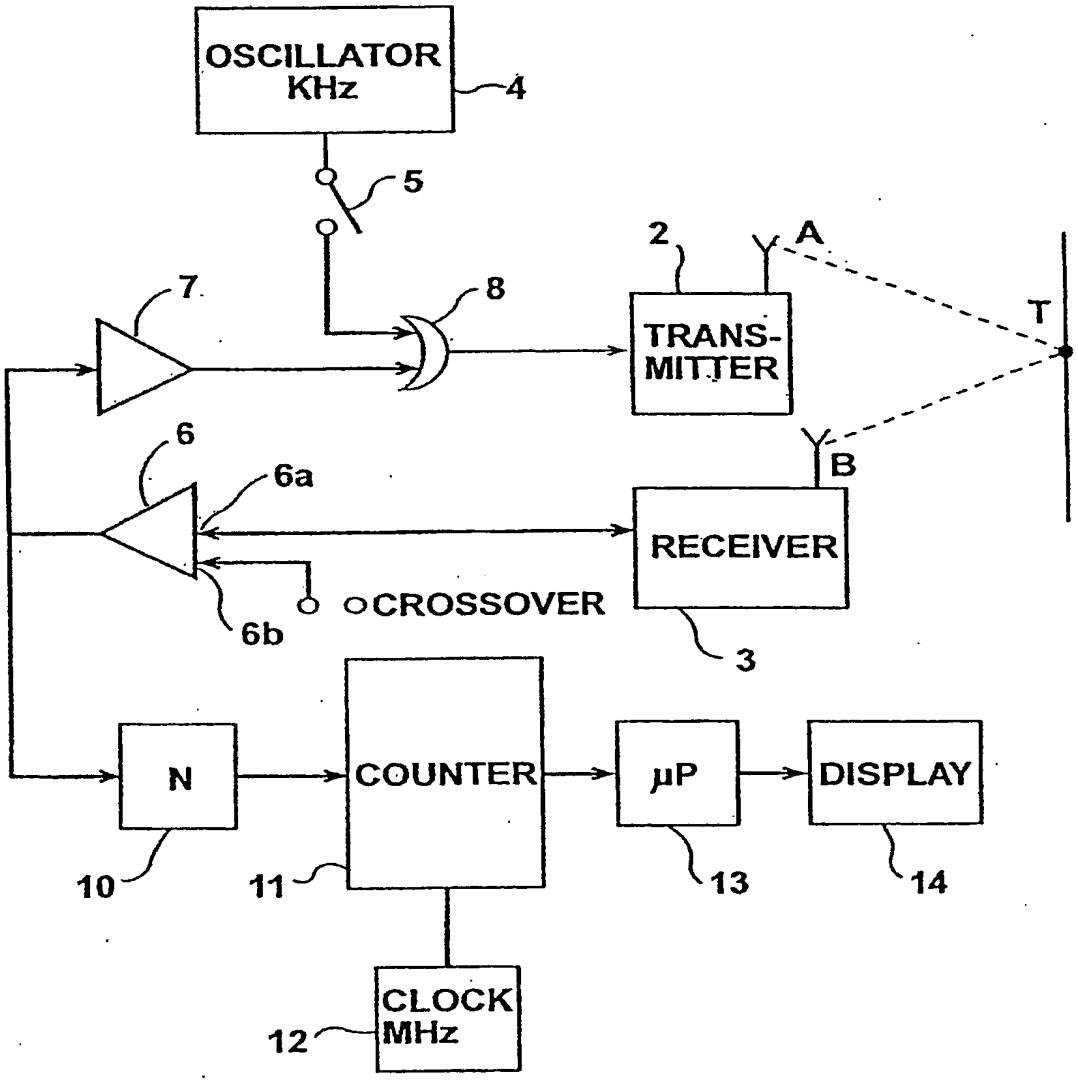

OSCILLATOR
KHz
4
5
2
A
7
8
TRANS-
MITTER
T
6
6a
B
RECEIVER
6b
CROSSOVER
3
N
COUNTER
µP
DISPLAY
10
11
13
14
CLOCK
MHz
12

Fig. 1

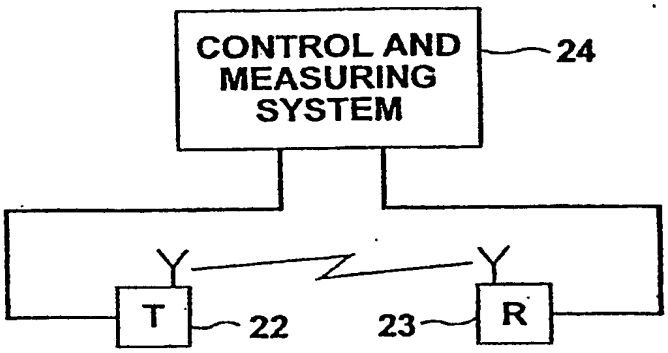


Fig. 2

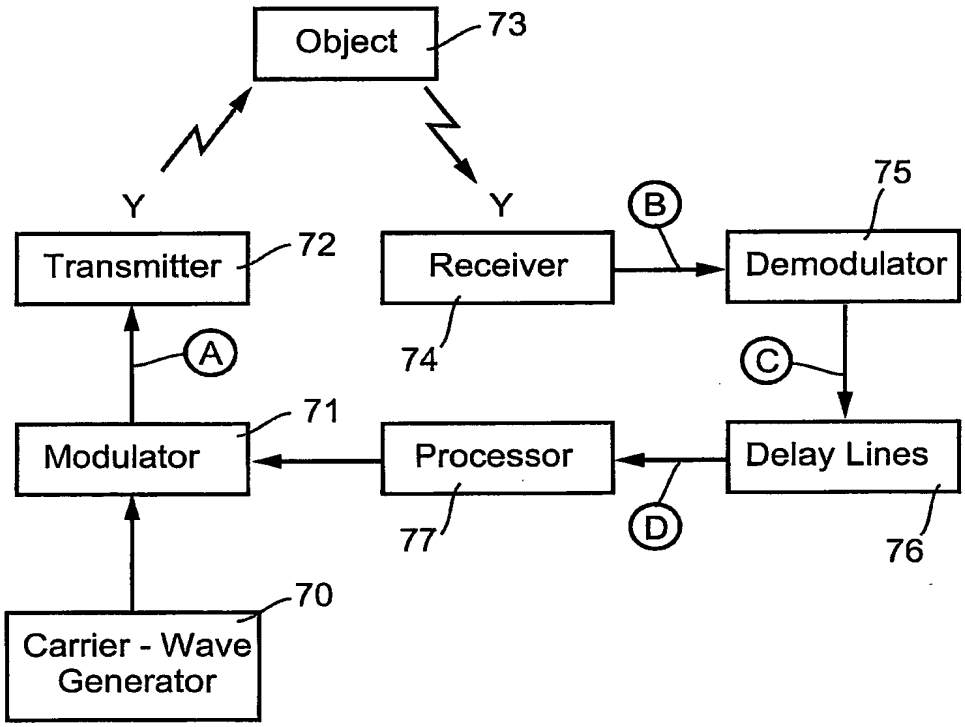

Object
73
Y
Y
Transmitter
72
Receiver
B
Demodulator
75
74
A
C
Modulator
71
Processor
Delay Lines
77
D
76
Carrier - Wave Generator
70

Fig. 3

Fig. 4a

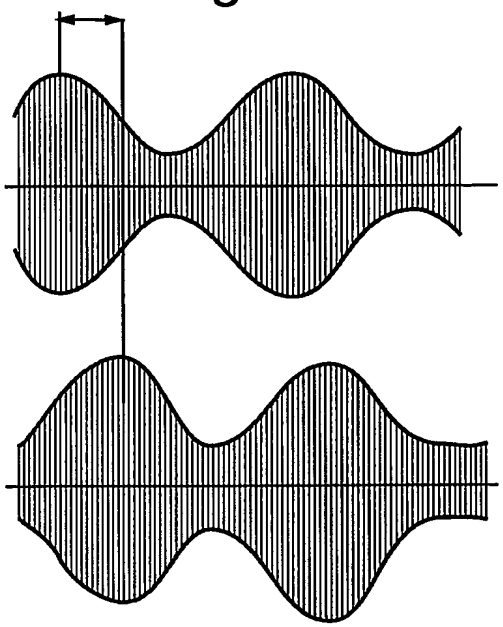


Fig. 4b

Fig. 4c

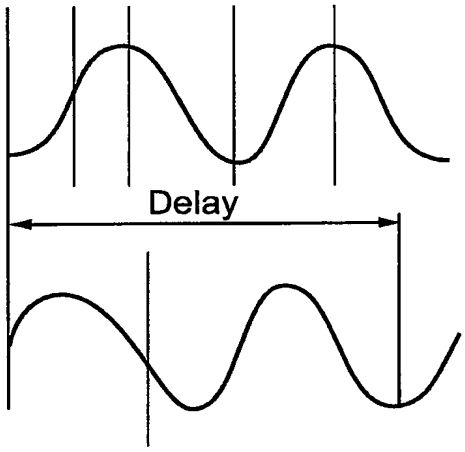


Fig. 4d

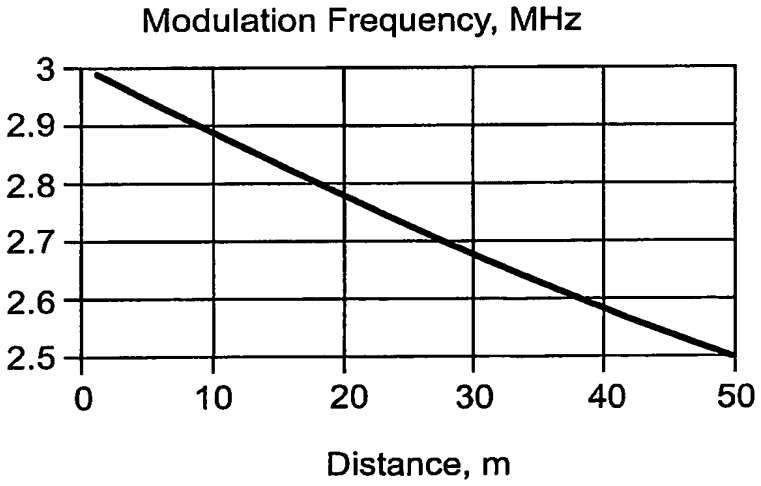
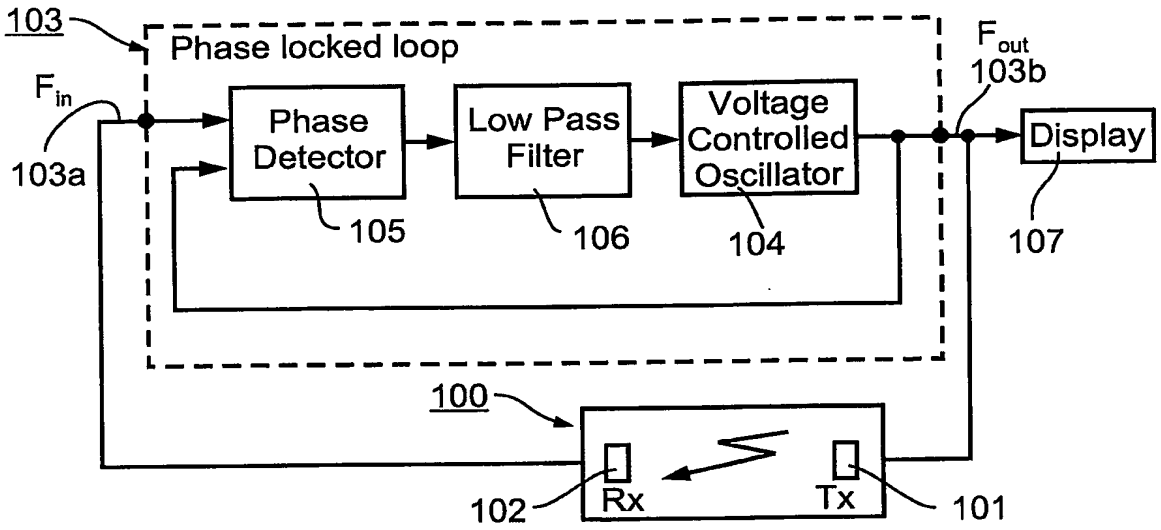


Fig. 5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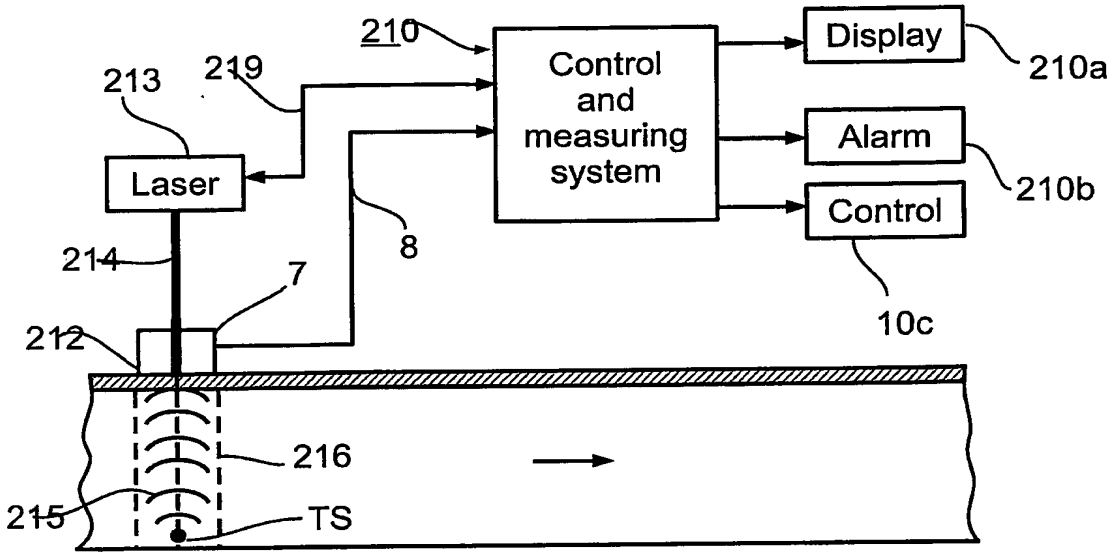
Phase locked loop
F_{in}
103a
Phase Detector
Low Pass Filter
Voltage Controlled Oscillator
105
106
104
F_{out}
103b
Display
107
100
Rx
Tx
102
101

Fig. 6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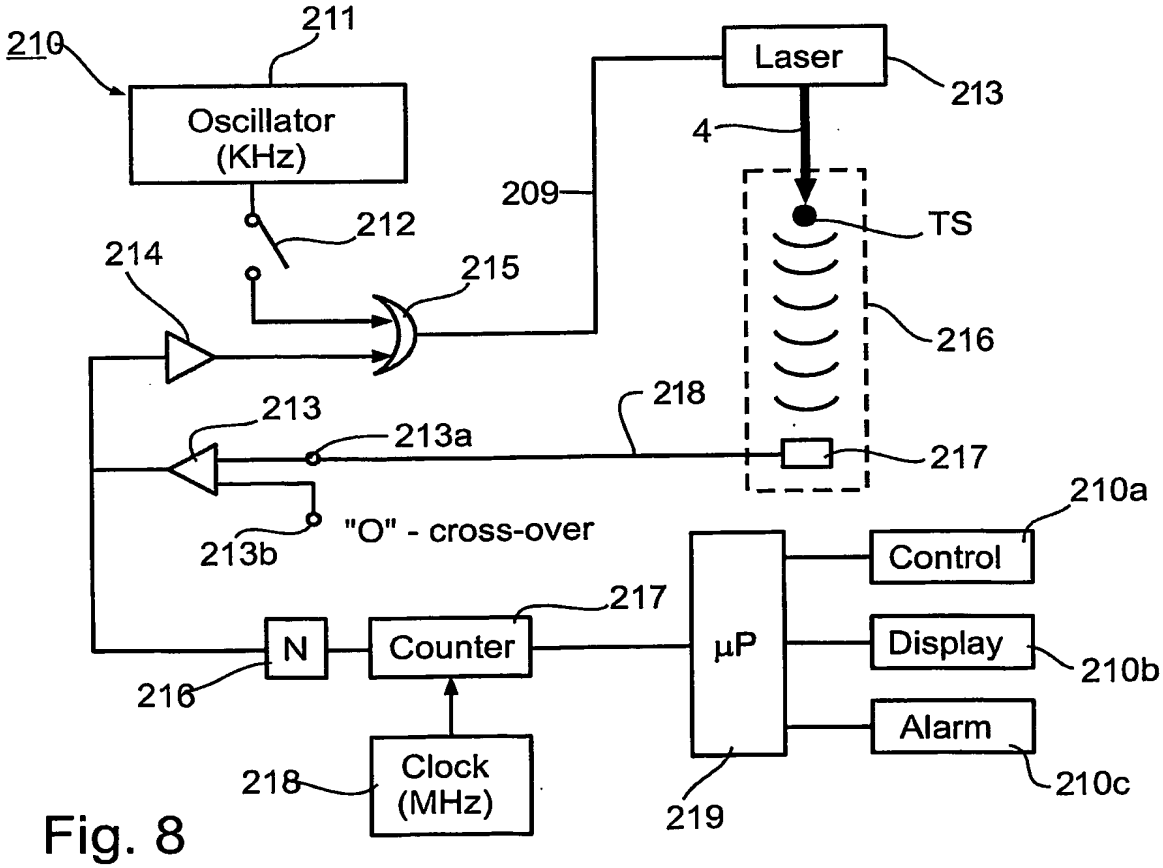
Control and measuring system
Display
210a
Alarm
210b
Control
10c
213
219
Laser
214
7
8
212
216
215
TS

Fig. 7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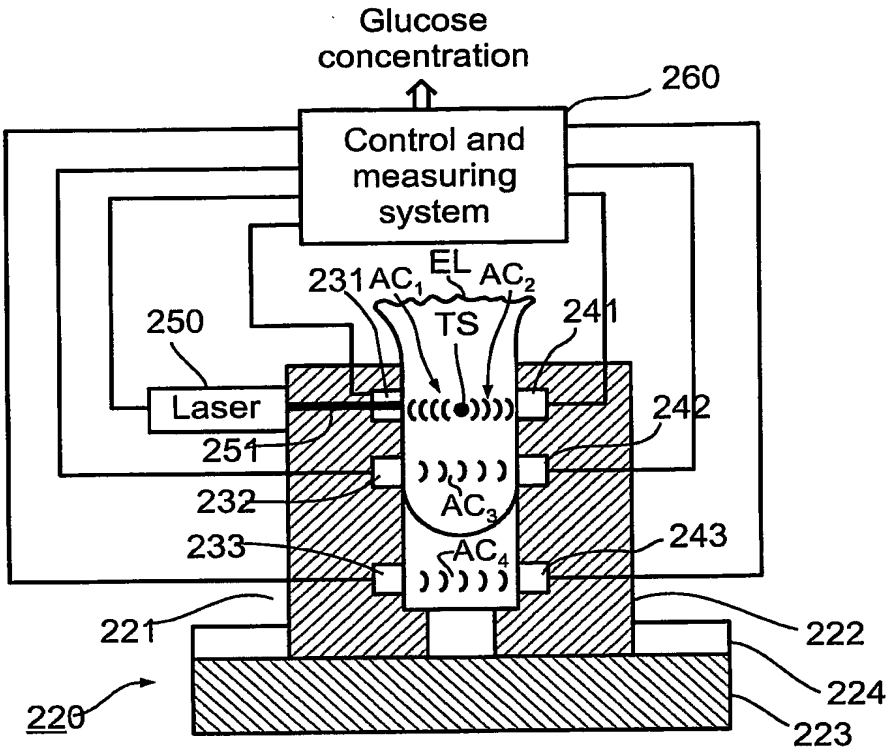
211
Oscillator (KHz)
212
214
215
209
Laser
213
4
TS
216
213
213a
218
217
213b
"O" - cross-over
210a
Control
217
N
Counter
µP
Display
210b
216
Alarm
218
Clock (MHz)
219
210c

Fig. 8


Glucose concentration
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Control and measuring system
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AC1
EL
AC2
TS
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Laser
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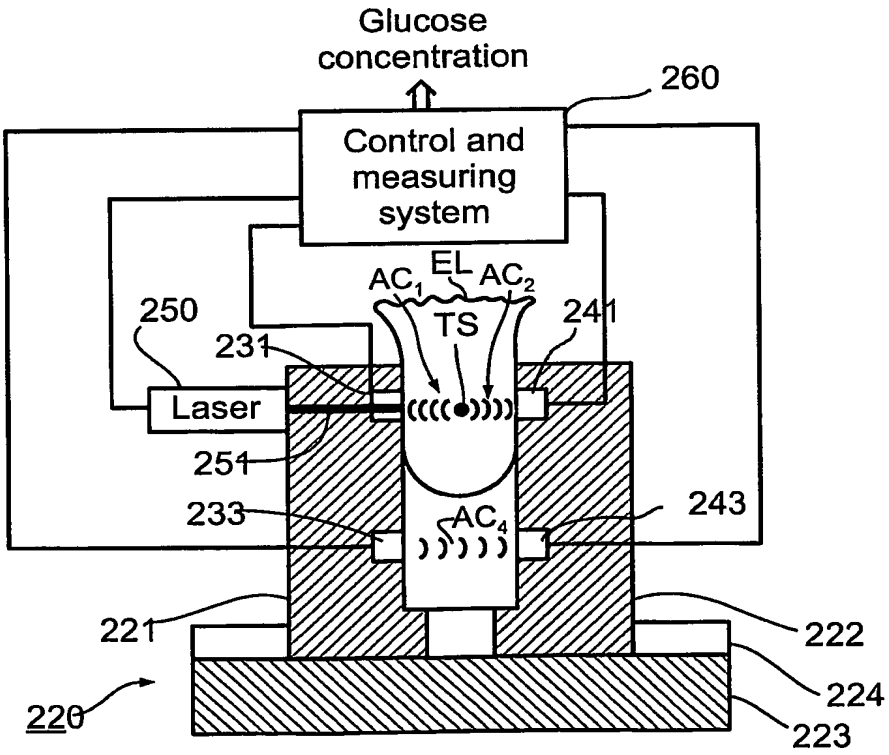
251
232
AC3
233
AC4
243
221
222
224
220
223

Fig. 9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Control and measuring system
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EL
AC2
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AC4
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222
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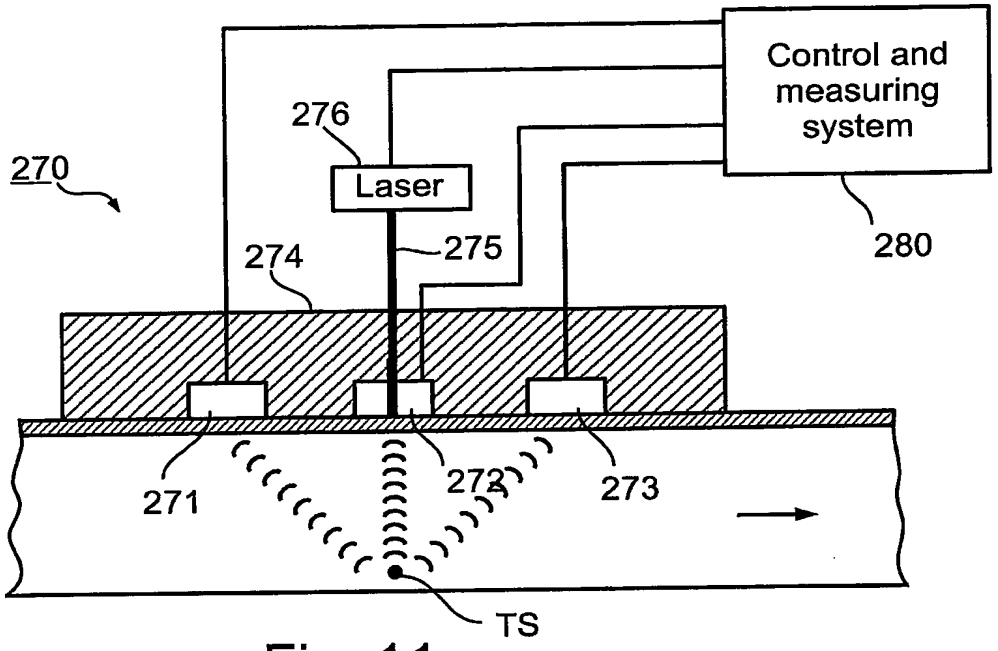
220
223

Fig. 10


Control and measuring system
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Laser
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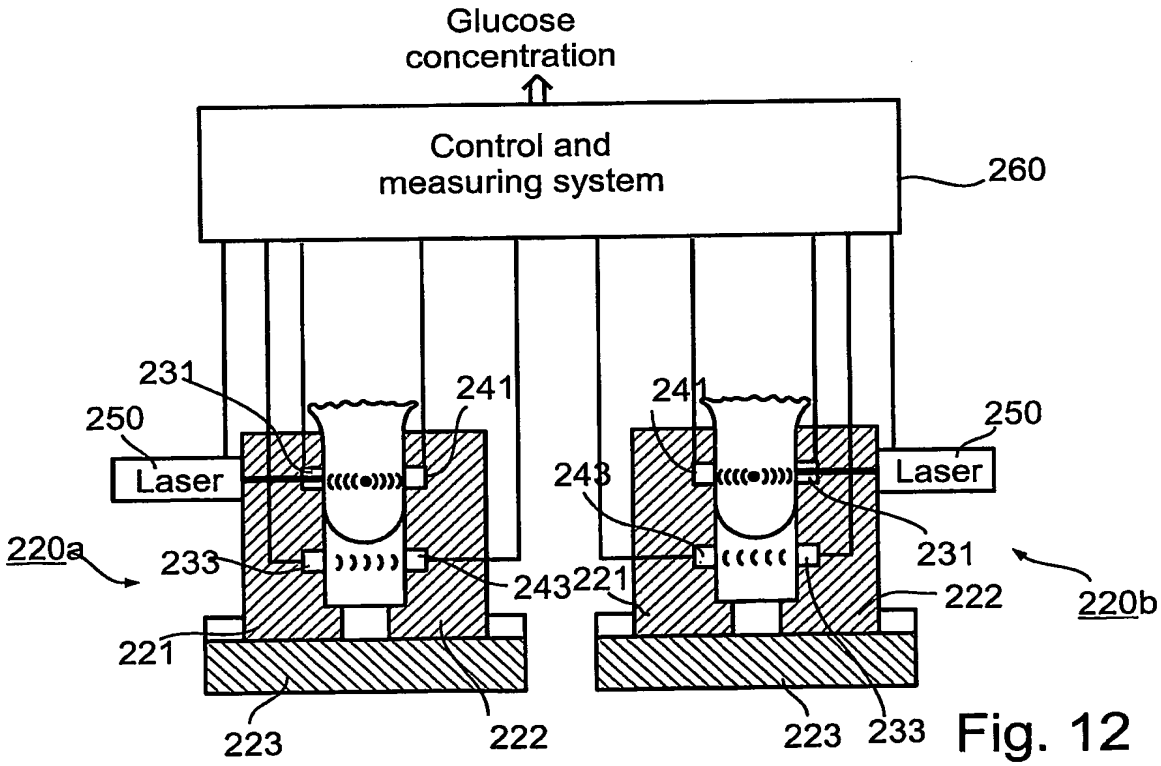
274
275
280
271
272
273
TS

Fig. 11


Glucose concentration
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Laser
Laser
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220a
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231
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220b
221
223
222
223
233

Fig. 12